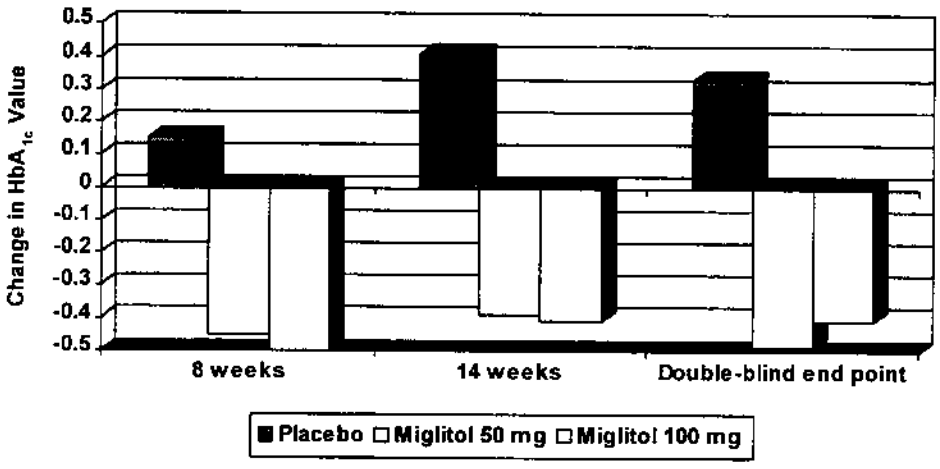
Figure 1: Changes from Baseline HbA_{1C} in Type 2 Diabetes Mellitus, Who Had Inadequate Metabolic Responses to Maximum Doses of an Oral Sulfonylurea, Treated with Miglitol:



Despite the improvements in laboratory parameters, no changes in body weight or dietary composition were observed. Patients receiving the 100 mg dose did experience a greater number of side effects. The improvements in laboratory results seen in this study do indicate that miglitol is a useful adjunctive agent in the management of diabetes mellitus in patients inadequately controlled with diet and oral sulfonylurea therapy.

A long-term, double-blind, placebo controlled study also evaluated miglitol as monotherapy compared to glyburide in 411 patients 60 years of age or older with Type 2 diabetes. Patients were treated with diet alone for at least 12 weeks prior to randomization. Patients received either placebo three times daily, miglitol 25 mg three times daily, miglitol 50 mg three times daily or glyburide once daily at a dose titrated based on fasting plasma glucose. Therapy was continued for 56 weeks. Results are summarized in Table 3. No difference between placebo and the active treatments, or between active treatments, was observed with regard to triglycerides, urinary glucose excretion, or urinary albumin excretion. Diarrhea, flatulence, nausea and vomiting occurred more frequently in the miglitol-treated patients, while symptomatic hypoglycemia and cardiovascular events (eg, peripheral edema, stroke, coronary artery disorder) occurred more frequently in the glyburide-treated patients. Glyburide-treated patients experienced a mean gain of 2.3 kg over the course of the study, while placebo- and miglitol-treated patients experienced weight reductions (1.5 to 2.3 kg). Similar results were obtained in a 6-month study comparing miglitol 50-100 mg three times daily, glyburide 3.5 mg once or twice daily and placebo in 119 patients with Type 2 diabetes inadequately treated with diet alone. HbA_{1C} was reduced 0.75 in the miglitol group and 1.01 in the glyburide group. Fasting and postprandial blood glucose were reduced in both the miglitol and glyburide groups. Gastrointestinal side effects occurred more frequently in the miglitol-treated patients, while hypoglycemia and weight gain occurred more frequently in the glyburide-treated patients.

Table 3: Miglitol and Glyburide Comparative Study:

	Mean Change from Baseline			
Parameter	Placebo	Miglitol 25 mg TID	Miglitol 50 mg TID	Glyburide
HbA_{1C} (%)	-0.01**	-0.5***	-0.41***	-0.93
Fasting plasma glucose (mg/dL)	1**	-13.4***	-19.4	-30.5
60-min. plasma glucose (mg/dL)	0.6**	-43.9	-57.8***	-32.5
Plasma glucose AUC (mg*min/dL)	716**	-3361	-5462	-3615
Fasting serum insulin (mcU/mL)	0.63***	-0.88***	-0.05***	3.59
60-min. serum insulin (mcU/mL)	-0.34**	-11.7***	-12.9***	12.7
Serum insulin AUC (mcU*min/mL)	79**	-863***	-1268***	1896

** significantly different from miglitol and glyburide ($p<0.05$)
*** significantly different from glyburide ($p<0.05$)

Miglitol and glyburide were also compared in a 6-month, double-blind study enrolling 100 patients with Type 2 diabetes treated with diet and exercise. Following a 7-week placebo run-in period, patients were assigned treatment with either miglitol 50 mg three times daily for 6 weeks and then 100 mg three times daily for the next 18 weeks or glyburide 2.5 mg twice daily for 6 weeks and then 5 mg twice daily for the next 18 weeks. Both treatments produced a reduction in HbA_{1C}, fasting blood glucose and postprandial serum glucose.

Miglitol was also compared with placebo in the treatment of 345 African-American patients with Type 2 diabetes previously treated with either diet alone or sulfonylureas. Patients received either placebo or miglitol 50 or 100 mg three times daily for 1 year. Diet and sulfonylurea dosages were held constant during the study. HbA_{1C}, postprandial plasma glucose and fasting plasma glucose were all reduced on miglitol therapy compared to placebo. HbA_{1C} dropped 0.53 after 28 weeks of miglitol therapy and by 0.21 at the end of 1 year, while in the placebo group the HbA_{1C} was increased 0.66 at 28 weeks and 0.53 at week-52. HbA_{1C} was 1.84 lower in the miglitol group than the placebo group among patients treated with diet alone and 0.68 lower in the miglitol group than the placebo group among patients treated with maximal doses of sulfonylureas.

Another study evaluating miglitol in 102 patients with Type 2 diabetes treated with diet and/or sulfonylureas emphasized the importance of compliance with the regimen in achieving a therapeutic benefit. Following a 4-week placebo run-in period, patients were treated with either placebo or miglitol 100 mg three times daily with the first bite of the three main meals for 18 weeks. A constant diet and sulfonylurea dose was maintained throughout the study. Sulfonylureas were used in 75% of patients during the study. Miglitol was more effective than placebo in reducing HbA_{1C} and reducing fasting blood glucose levels. Among patients completing the study without protocol violations, HbA_{1C} was 7.27% in the miglitol group compared to 8.05% in the placebo group after 18 weeks of therapy ($p=0.0158$). Miglitol was not more effective than placebo in patients who completed the 18-week trial but had poorer compliance with the regimen.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:

Because the absorption of sucrose is delayed by miglitol, episodes of hypoglycemia should be treated with oral glucose (dextrose) instead of sucrose (cane sugar).

Miglitol is excreted in human milk at very low levels. Although estimated exposure to a nursing infant is 0.4% of the maternal dose, use of miglitol in nursing mothers is not recommended.

ADVERSE REACTIONS: The most common adverse reactions observed with miglitol are very similar to

those reported with acarbose. These adverse effects are intestinal gas (eg, borborygmus, flatulence), nausea, soft stools or diarrhea and abdominal pain or discomfort. The frequency and severity are dose related and decrease with time. Some investigators have reported that the incidence of gastrointestinal side effects appeared lower with miglitol than with acarbose; however, comparative studies would be necessary to determine a difference (see Table 5). Intestinal side effects have been described as directly proportional to sucrose intake. Other reported adverse effects with miglitol have included skin rashes and low serum iron. Elevations in serum transaminases have not been observed with miglitol.

Table 5: Comparison of Adverse Effects Reported in the Product Labeling of Acarbose and Miglitol:

	Acarbose Labeling		**Miglitol Labeling**	
Adverse Effect	**Acarbose (n=1075)**	**Placebo (n=818)**	**Miglitol (n=962)**	**Placebo (n=603)**
Abdominal pain	21%	9%	11.7%	4.7%
Diarrhea	33%	12%	28.7%	10%
Flatulence	77%	32%	41.5%	12%

DRUG INTERACTIONS: When acarbose or miglitol therapy is initiated in individuals already receiving an oral hypoglycemic or insulin, the blood glucose levels should be monitored closely since hypoglycemia may develop. If hypoglycemia develops, a reduction in the dose of the oral hypoglycemic or insulin may be necessary. In addition, the administration of insulin could be given immediately before the meal in individuals treated with miglitol, instead of 30 to 60 minutes prior to eating.

Miglitol appears to lower the AUC and peak concentrations of glyburide and metformin during concomitant therapy; however, the reductions in glyburide and metformin levels do not appear clinically important.

Digoxin plasma concentrations were reduced in healthy volunteers receiving concomitant miglitol and digoxin, but not in diabetic patients on digoxin who were treated with miglitol. Monitoring of digoxin levels may be advisable following the initiation or discontinuation of miglitol therapy. Miglitol may also reduce the bioavailability of ranitidine and propranolol. Miglitol does not affect the pharmacokinetics or pharmacodynamics of warfarin or nifedipine.

Acarbose, in contrast, does not affect the pharmacokinetics or pharmacodynamics of digoxin, nifedipine, propranolol or ranitidine. It also does not interfere with the absorption or disposition of glyburide.

Intestinal adsorbents (eg, charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (eg, amylase, pancreatin) may reduce miglitol efficacy. Concomitant administration should be avoided. Antacid administration did not affect miglitol pharmacokinetics.

RECOMMENDED MONITORING: When acarbose or miglitol therapy is initiated in individuals already receiving an oral hypoglycemic or insulin, the blood glucose levels should be monitored closely since reduction in blood glucose levels, including hypoglycemia, may develop. Therapy in all patients should be monitored with periodic blood glucose tests and measurement of glycosylated hemoglobin levels approximately every 3 months.

DOSING: Miglitol should be taken orally three times daily at the start (with the first bite) of each main meal. The dose should be individualized based on effectiveness and tolerability while not exceeding the maximum recommended dosage of 100 mg three times daily. Therapy should be initiated at a dosage of 25 mg three times daily and the dose gradually increased. Some patients may require initiation of therapy with 25 mg once daily to minimize gastrointestinal side effects, with the frequency of administration gradually increased to three times daily. One-hour postprandial plasma glucose determinations may be used to determine the therapeutic response to miglitol and establish the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured approximately every 3 months to assess the therapeutic effectiveness. The usual maintenance dose is 50 mg three

times daily. These general dosing guidelines are very similar to those of acarbose, which is also dosed three times daily with meals and initiated at a dosage of 25 mg three times daily.

Despite the favorable results obtained with the addition of acarbose or miglitol to diet or diet plus oral hypoglycemic agents, they do not appear to be suitable substitutes for oral hypoglycemic therapy. NIDDM patients inadequately controlled with an oral agent switched to acarbose therapy show deterioration in glycemic control.

PRODUCT AVAILABILITY: Bayer received FDA approval for miglitol in December 1996; however, Bayer opted not to market the product. Pharmacia & Upjohn acquired the rights to market miglitol both as a prescription product, and possibly as an over the counter product in the future. Miglitol is available as 25 mg, 50 mg and 100 mg tablets in bottles of 100, bottles of 1000, and unit-dose packages of 100. Acarbose is also available as 25 mg, 50 mg, and 100 mg tablets in bottles of 100 and unit-dose packages of 100.

25mg - $0.49 AWP
50mg - $0.58 AWP
100mg - $0.66 AWP

CONCLUSION: Acarbose and miglitol are not cures for diabetes mellitus nor are they substitutes for diet, exercise, oral hypoglycemic agents or insulin. Instead, they appear to be worthwhile adjunctive agents in the management of diabetes mellitus. Whether acarbose or miglitol should be used prior to the initiation of oral hypoglycemics or insulin in NIDDM patients will require more clinical experience. Until then, acarbose and miglitol are reasonable adjunctive agents for patients unable to achieve adequate glycemic control with oral hypoglycemic or insulin therapy in combination with diet and exercise or in patients unwilling to try oral hypoglycemic or insulin therapy first. Whether miglitol offers any real advantages over acarbose remains to be proven. However, some patients may be able to tolerate one of the agents better than the other.

CANDESARTAN CILEXETIL- ATACAND® (Astra Merck)-1S

INDICATIONS: Candesartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. See Table 1 for a list of approved indications for the angiotensin receptor antagonists.

Table 1: Comparison of FDA-Approved Indications for the Angiotensin Receptor Antagonists:

Drug	Trade Name	Company	FDA-Approved Indication(s)	Date of FDA Approval
Candesartan	*Atacand*	Astra Merck	Hypertension	June 1998
Irbesartan	*Avapro*	Bristol-Myers Squibb & Sanofi	Hypertension	September 1997
Losartan	*Cozaar*	Merck	Hypertension	April 1995
Valsartan	*Diovan*	Novartis	Hypertension	December 1996

CLINICAL PHARMACOLOGY: Candesartan cilexetil (TCV-116) is a prodrug hydrolyzed to candesartan (CV-11974) during absorption from the gastrointestinal tract. Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist. The affinity of the active metabolite (candesartan) is 30 to 100-fold higher than the parent drug (candesartan cilexetil). It is 10 to 100 times more potent than losartan and its active metabolite (EXP3174). Its prolonged activity appears to be due to slow dissociation from angiotensin AT_1 receptors. Its activity has been more persistent than that of losartan.

In clinical trials, the antihypertensive effect was observed within 2 weeks of initial dosing, with full effect apparent within 4 weeks. Trough to peak ratios of blood pressure effect were generally over 80% with once-daily dosing, indicating blood pressure control was maintained over the 24-hour dosing interval. Peak blood pressure effects have been observed approximately 8 hours after oral administration.

No changes in serum levels of total cholesterol, triglycerides, glucose or uric acid have been observed during candesartan therapy. Candesartan did not alter the HbA_{1c} in patients with type 2 diabetes. Changes in heart rate have also not been observed in patients treated for hypertension.

The results of animal studies suggest candesartan may protect against proteinuria, renal tissue damage and glomerular injury associated with diabetes, hypertensive nephropathy and chronic renal failure. Candesartan has demonstrated more potent protective effects against the progression of renal injury than enalapril. A favorable renal profile has also

been seen in patients with hypertension.

PHARMACOKINETICS: Candesartan cilexetil is rapidly and completely converted to candesartan by ester hydrolysis during absorption. Following oral administration of candesartan cilexetil, the absolute bioavailability of candesartan is approximately 15%. Peak candesartan levels are reached after 3 to 4 hours. Plasma concentrations of candesartan cilexetil are not detectable. Candesartan bioavailability is not affected by administration of candesartan cilexetil with food.

In the elderly, peak candesartan levels have been approximately 50% higher and the AUC approximately 80% higher than in younger subjects administered the same dose. However, with once-daily administration, accumulation has not been observed. Candesartan levels have also been elevated in patients with renal insufficiency. In patients with severe renal impairment (CrCl < 30 mL/min/1.73 m^2), the peak concentration and AUC have been increased approximately doubled. No differences in the pharmacokinetics of candesartan have been observed in patients with mild-to-moderate hepatic impairment. Initial dosage adjustments due to pharmacokinetic changes are not necessary in the elderly, patients with renal impairment or patients with mild hepatic disease.

Table 2: Comparative Pharmacokinetics:

	Candesartan	Irbesartan	Losartan	Valsartan
Prodrug	Yes*	No	Yes**	No
Time to peak (h)	3-4	1.5-2	1 / 2-4**	2-4
Bioavailability	15%	60-80%	33%	25%
Food - peak levels	–	No effect	Decreased	↓ 50%
Food - AUC	No effect	No effect	10%	↓ 40%
Elimination half-life (h)	9	11-15	2 / 6-9**	6
Elimination altered in renal dysfunction	Yes ***	No	No	No
Elimination altered in hepatic dysfunction	No	No	Yes	Yes
Protein binding	>99%	90%	~99%	95%

* candesartan cilexetil active metabolite candesartan
** losartan active metabolite EXP3174
*** dosage adjustments are not necessary

COMPARATIVE EFFICACY: In clinical trials, candesartan cilexetil 4 to 8 mg daily was

as effective as enalapril 10 to 20 mg. At 8 mg, candesartan cilexetil was as effective as losartan 50 mg, amlodipine 5 mg and hydrochlorothiazide 25 mg. Additive activity was demonstrated when candesartan cilexetil was used in combination with amlodipine or hydrochlorothiazide.

Candesartan cilexetil was compared with losartan in the treatment of essential hypertension using a multicenter, double-blind, placebo controlled design. The study enrolled 337 patients with essential hypertension. All previous antihypertensive medications were discontinued before enrollment in the study. A placebo run-in was done for the first 4 weeks of the study. If the patients' sitting diastolic blood pressure was between 95 to 114 mmHg at the end of the placebo run-in, the patient was randomized to the study medication. The study medications were candesartan cilexetil 8 mg (n=82), candesartan cilexetil 16 mg (n=86), losartan 50 mg (n=84) and placebo (n=85). The study medications were administered once daily in the morning for 8 weeks. Blood pressure and heart rate measurements were done with a fully automatic device during the morning clinic visit and ~24 hours after intake of the study drug. The diastolic blood pressure was decreased by 8.9 mmHg with candesartan cilexetil 8 mg, 10.3 mmHg with candesartan cilexetil 16 mg and 6.6 mmHg with losartan 50 mg and increased slightly with placebo. The active medications were all better than placebo in reducing the sitting diastolic blood pressure. There was no difference between the candesartan cilexetil 8 mg and the losartan 50 mg in reduction in blood pressure. The mean difference between the sitting diastolic blood pressure with candesartan cilexetil 16 mg and losartan 50 mg was 3.7 mmHg (p=0.013).

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:

Symptomatic hypotension may occur in patients who are volume- and/or salt-depleted, such as patients receiving high- dose diuretics or patients on dialysis. Volume depletion should be corrected prior to initiation of candesartan therapy or therapy should be initiated with a low dose under close supervision. Candesartan should also be administered with caution in patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system.

Candesartan is categorized in Pregnancy Categories C (first trimester) and D (second and third trimesters). Administration of medications directly acting on the renin-angiotensin system has been associated with fetal and neonatal injury and death following exposure during the second or third trimesters. Adverse effects do not appear to have resulted from exposure limited to the first trimester. When pregnancy is detected, candesartan therapy should be discontinued as soon as possible.

Breast feeding women should discontinue either candesartan or nursing.[1] This recommendation regarding breast feeding applies to all the angiotensin II receptor antagonists and is not unique to candesartan.

ADVERSE REACTIONS: Candesartan has been well tolerated in clinical trials. The most common side effects (occurring in more than 1% of patients) have included fatigue, peripheral edema, back pain, chest pain, headache, dizziness, upper respiratory tract infection, pharyngitis, rhinitis, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia and albuminuria. Small increases in creatinine, blood urea nitrogen, potassium, liver enzymes and serum bilirubin have been observed rarely in clinical trials, as have hyperuricemia and reductions in hemoglobin and hematocrit.

DRUG INTERACTIONS: Drug interactions have not been reported between candesartan and glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide and oral contraceptives in clinical trials. In addition, since candesartan is not metabolized by the cytochrome P450 system and does not affect P450 enzymes, interactions associated with this enzyme system are not anticipated.

DOSING: The usual recommended starting dose is 16 mg once daily when used as monotherapy in patients who are not volume depleted. Blood pressure response is dose-related over the range of 2 to 32 mg. Candesartan can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Initial dosage adjustments are not necessary in the elderly, patients with mild renal impairment or patients with mild hepatic impairment. For patients with possible volume depletion, therapy should be administered under close supervision with consideration to the use of a reduced dose. Table 4 contains a comparison of the doses of the available angiotensin II receptor antagonists.

Table 4: Comparative Doses:

	Candesartan	Irbesartan	Losartan	Valsartan
Dosage range	8 - 32 mg/day; once or twice daily	75 - 300 mg once daily	25 - 100 mg/day once or twice daily	80 - 320 mg once daily
Recommended initial dose	16 mg once daily	150 mg once daily	50 mg once daily	80 mg once daily
Maximum dose	32 mg/day; once or twice daily	300 mg once daily	100 mg/day; once or twice daily	320 mg once daily
Dose in volume- or salt-depleted patients	no dosage recommendation*	75 mg once daily	25 mg once daily	no dosage recommendation**

* manufacturer recommends therapy be initiated under close medical supervision with consideration given to administration of a lower dose

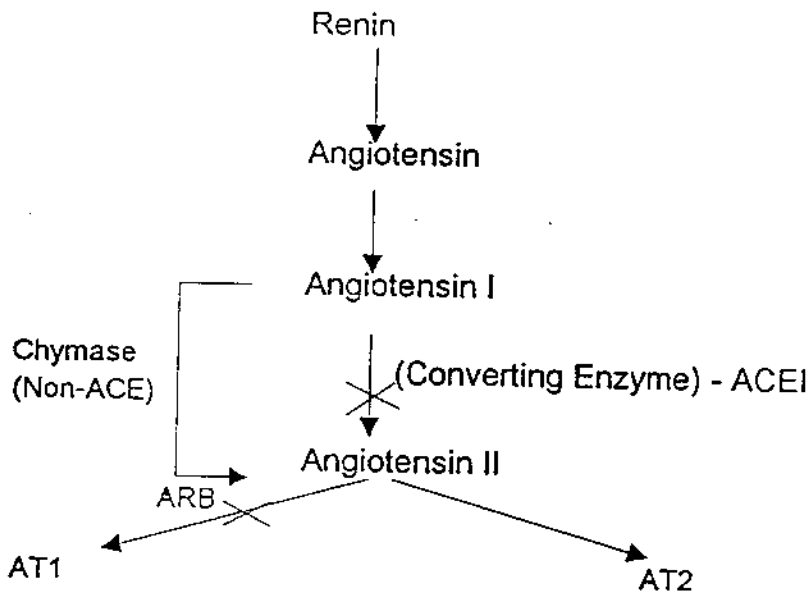
** manufacturer recommends correcting condition prior to initiating treatment with valsartan or initiating therapy under close medical supervision

PRODUCT AVAILABILITY: Candesartan received FDA approval in June 1998. It is available as 4, 8, 16 and 32 mg tablets. Table 5 summarizes the dosage forms available for the angiotensin receptor antagonists.

Table 5: Available Dosage Forms for the Angiotensin Receptor Antagonists.

	Candesartan	Irbesartan	Losartan	Valsartan
Strengths Available	4, 8, 16 and 32 mg	75, 150 and 300 mg	25, 50 mg	80, 160 mg
Tablet/Capsule	Unscored tablet	Unscored tablet	Unscored tablet	Capsule

CONCLUSION: Candesartan is another angiotensin II AT_1 receptor antagonist. It provides an alternative to irbesartan, losartan and valsartan, but at this time demonstrates no apparent advantage over these agents. Like the other agents in this class, candesartan is only approved for the treatment of hypertension. It is unknown whether candesartan will be as effective as angiotensin converting enzyme inhibitors in the treatment of congestive heart failure or prevention of proteinuria in patients with diabetes.



Adrenals - release of aldosterone, epinephrine, norepinephrine

Blood vessels - vasoconstriction, growth and proliferation, angiogenesis

Heart - hypertrophy, inotrope

Kidney - stimulation of Na+ and H2O reabsorption, inhibition of renin release

Pituitary -release of vasopressin (ADH)

Antiproliferative effect

Release of Nitric Oxide

Vasodilation

Apoptosis/increases programmed cell death and cell differentiation

Antidiuresis

(The AT2 receptor is usually only expressed in high density during fetal life and in lesser amounts in adults. It is upregulated or re-expressed in patients with vascular injury, MI, and CHF.)

TELMISARTAN - MICARDIS™ (Boehringer Ingelheim/Abbott) 1S

INDICATIONS: Telmisartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. See Table 1 for a list of approved indications for the angiotensin receptor antagonists.

Table 1: Comparison of FDA-Approved Indications for the Angiotensin II Receptor Antagonists:

Drug	Trade Name	Company	FDA-Approved Indication	Date of FDA Approval
Candesartan	*Atacand*	Astra Merck	Hypertension	June 1998
Irbesartan	*Avapro*	Bristol-Myers Squibb & Sanofi	Hypertension	September 1997
Losartan	*Cozaar*	Merck	Hypertension	April 1995
Telmisartan	*Micardis*	Boehringer Ingelheim	Hypertension	November 1998
Valsartan	*Diovan*	Novartis	Hypertension	December 1996

CLINICAL PHARMACOLOGY: Telmisartan is an orally active, specific and selective, competitive nonpeptide angiotensin II AT_1 receptor antagonist. It is a non-biphenyl tetrazole derivative. Irbesartan and losartan are biphenyl tetrazole derivatives, while valsartan is a non-heterocyclic angiotensin II antagonist.

Blood pressure reductions are observed within 3 hours after administration of a single telmisartan dose. At doses of 20 mg, 40 mg and 80 mg, the antihypertensive effect is maintained over a 24-hour interval with once-daily dosing. Telmisartan 80 mg inhibited the pressor response to an angiotensin II infusions by about 90% at peak plasma concentrations, with approximately 40% inhibition persisting for 24 hours. In patients with hypertension, no changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance have been observed. Unlike losartan, telmisartan does not exert an uricosuric effect. Aldosterone levels were unaltered in healthy subjects.

PHARMACOKINETICS: Peak telmisartan levels are reached within 0.5 to 1 hour after oral administration. The absolute bioavailability of telmisartan is dose dependent. Following a 40 mg dose, bioavailability is 42%; following a 160 mg dose, bioavailability is 58%. Food slightly reduces the bioavailability. Telmisartan is greater than 99.5% plasma protein bound.

Terminal elimination half-life is approximately 24 hours. Greater than 97% of the administered telmisartan dose is eliminated unchanged in the feces via biliary excretion. A small portion of telmisartan is metabolized to a single inactive glucuronide conjugate. Cytochrome P450 isozymes are not involved in the metabolism of telmisartan. See Table 2 for a comparison of the pharmacokinetic parameters of the available angiotensin receptor antagonists.

Telmisartan pharmacokinetics do not differ between elderly patients and those younger than 65 years. Plasma levels are two to three times higher in females compared to males, although clinical differences have not been observed and dosage adjustments are not necessary. The pharmacokinetics of telmisartan are not altered in patients with renal dysfunction. Plasma concentrations are increased and absolute bioavailability is close to 100% in patients with hepatic insufficiency. Telmisartan should be used with caution in this patient population. Pharmacokinetics of telmisartan have not been evaluated in children.

Table 2: Comparative Pharmacokinetics of Angiotensin II Receptor Antagonists:

	Candesartan	Irbesartan	Losartan	Telmisartan	Valsartan
Prodrug	Yes*	No	Yes**	No	No
Time to peak (hr)	3-4	1.5-2	1 / 2-4**	0.5-1	2-4
Bioavailability	15%	60-80%	33%	42-58%	25%
Food - Peak Levels	–	No effect	9	–	9 50%
Food - Area-Under-The-Curve	No effect	No effect	9 10%	9 6-20%	9 40%
Elimination half-life (hr)	9	11-15	2 / 6-9**	24	6
Elimination altered in renal dysfunction	Yes ***	No	No	No	No
Elimination altered in hepatic dysfunction	No	No	Yes	Yes	Yes
Protein binding	>99%	90%	~99%	>99.5%	95%

* Candesartan cilexetil: active metabolite candesartan
** Losartan: active metabolite EXP3174
*** Dosage adjustments are not necessary

COMPARATIVE EFFICACY: Very little information is published on the effectiveness and safety of telmisartan. Results of six studies evaluating telmisartan as monotherapy or in conjunction with hydrochlorothiazide are summarized in the package insert. A total of 1,031 patients received telmisartan and 742 received placebo in these trials. Once-daily telmisartan doses effectively reduced systolic and diastolic blood pressure by 6-8 mmHg/6 mmHg at 20 mg, 9-13 mmHg/6-8 mmHg at 40 mg, and 12-13 mmHg/7-8 mmHg at 80 mg. Higher doses provide no additional blood pressure lowering benefit. Blood pressure reductions were observed after the first dose, with a maximal reduction by about 4 weeks. Further blood pressure reductions were observed when telmisartan was administered with hydrochlorothiazide. Telmisartan=s blood pressure lowering effects are less in black patients than Caucasian patients.

In one placebo controlled, double-blind study, telmisartan was evaluated at doses of 20 to 160 mg once daily for 4 weeks in patients with mild-to-moderate hypertension. All doses were more effective than placebo. Mean reductions from baseline ranged from 6.9 to 10.5 mmHg for diastolic blood pressure and 3.3 to 11.7 mmHg for systolic blood pressure. Trough-to-peak ratios for supine diastolic blood pressure were close to 100% at each dose level. Trough-to-peak ratios for supine systolic blood pressure were greater than 66% for doses greater than 20 mg and 49% at the 20 mg dose level. No additional blood pressure lowering effect was observed with doses greater than 80 mg.

Telmisartan was compared with enalapril in a placebo controlled trial enrolling 440 patients with mild-to-moderate hypertension. Following a placebo run-in period, patients were assigned therapy with telmisartan 40 mg, telmisartan 80 mg, telmisartan 120 mg, telmisartan 160 mg, enalapril 20 mg or placebo. All therapies were administered once daily for 12 weeks. All telmisartan doses and enalapril were more effective than placebo in reducing both systolic and diastolic blood pressure. Final blood pressure reductions ranged from 10-11.9 mmHg/8.6-9.7 mmHg on telmisartan and from 8.2 mmHg/7.2 mmHg on enalapril. Cough was reported in 4.2% of enalapril-treated patients compared to 0.3% of telmisartan-treated patients and 1.3% of placebo-treated patients. Efficacy comparable to amlodipine and losartan was also reported.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS: Telmisartan is contraindicated in patients who are hypersensitive to any component of the product (telmisartan, sodium hydroxide, meglumine, povidone, sorbitol and magnesium stearate).

Symptomatic hypotension may occur in patients who are volume- and/or salt-depleted, such as patients receiving high- dose diuretics or patients on dialysis. Volume depletion should be corrected prior to initiation of telmisartan therapy or therapy should be initiated under close medical supervision or with a low dose of an alternative angiotensin II antagonist due to the lack of availability of a lower strength of

telmisartan than 40 mg. The telmisartan product labeling states that telmisartan can not be administered at a dose of less than 40 mg. It may be possible to split the tablet immediately prior to administration. The tablet is extremely sensitive to moisture, so the other half of the tablet would have to be discarded rather than saved for a later dose. A 20 mg tablet will be available in the future.* [* Personal Communication. Maureen Oakes. Boehringer Ingelheim. 24 November 1998.]

Telmisartan should also be administered with caution in patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system.

Telmisartan is categorized in Pregnancy Categories C (first trimester) and D (second and third trimesters). Administration of medications directly acting on the renin-angiotensin system have been associated with fetal and neonatal injury and death following exposure during the second or third trimesters. Adverse effects do not appear to have resulted from exposure limited to the first trimester. When pregnancy is detected, telmisartan therapy should be discontinued as soon as possible. Telmisartan therapy should be continued during pregnancy only if no other alternative therapy is available. If oligohydramnios (abnormally small amount of amniotic fluid) is observed, telmisartan should be discontinued unless it is considered life-saving for the mother. Infants with a history of *in utero* exposure to telmisartan should be closely monitored for hypotension, oliguria and hyperkalemia. Breast feeding women should discontinue either telmisartan or nursing.

Safety and effectiveness in pediatric patients have not been established and pharmacokinetic studies have not been performed in the pediatric population.

ADVERSE REACTIONS: Telmisartan was well tolerated in clinical trials, with an incidence of side effects comparable to placebo. Adverse effects occurring in at least 1% of patients and at a higher incidence than with placebo included upper respiratory tract infection, back pain, sinusitis, diarrhea and pharyngitis. Cough was reported in 1.6% of telmisartan-treated patients and 1.6% of placebo-treated patients. Symptomatic orthostatic hypotension after the first dose occurred in 0.04% of patients in clinical trials. A complete list of the adverse reactions associated with telmisartan therapy can be found in the adverse reaction section of the product labeling. It is not possible to accurately compare the incidence of side effects of the angiotensin II AT_1 receptor antagonist because of the way the data are reported in the product labeling. However, all five agents are well tolerated, and the incidence of side effects is low with all five agents.

DRUG INTERACTIONS: Telmisartan coadministration resulted in increased digoxin peak plasma concentration (49%) and trough concentration (20%). Digoxin should be monitored when initiating, adjusting or discontinuing telmisartan. Telmisartan decreased warfarin trough plasma concentrations slightly, although INR was not altered.

Drug interactions have not been observed with acetaminophen, amlodipine, glyburide, hydrochlorothiazide or ibuprofen and are not anticipated with agents whose metabolism is dependent upon cytochrome P450. Telmisartan does exert some inhibitory effect on CYP2C19; therefore, inhibition of the metabolism of medications metabolized by CYP2C19 is possible (eg, diazepam, omeprazole).

DOSING: The recommended initial dose of telmisartan is 40 mg once daily. It may be administered with or without food. The maximum recommended dose is 80 mg once daily. Patients requiring additional blood pressure reduction may benefit from the addition of a diuretic. No dosage adjustments are necessary in patients with renal dysfunction or in the elderly. Table 4 compares the dosing recommendations for the angiotensin II receptor antagonists.

Telmisartan tablets should not be removed from the blister pack until immediately prior to administration.

Table 4: Comparative Doses of the Available Angiotensin II Receptor Antagonists:

	Candesartan	Irbesartan	Losartan	Telmisartan	Valsartan
Dosage range	8 - 32 mg/day; once or twice daily	75 - 300 mg once daily	25 - 100 mg/day once or twice daily	20 - 80 mg once daily	80 - 320 mg once daily
Recommended initial dose	16 mg once daily	150 mg once daily	50 mg once daily	40 mg once daily	80 mg once daily
Maximum dose	32 mg/day; once or twice daily	300 mg once daily	100 mg/day; once or twice daily	80 mg once daily	320 mg once daily
Dose in volume- or salt-depleted patients	No dosage recommendation *	75 mg once daily	25 mg once daily	No dosage recommendation **	No dosage recommendation ***

* manufacturer recommends therapy be initiated under close medical supervision with consideration given to administration of a lower dose

** manufacturer recommends correcting condition prior to initiating treatment with telmisartan, or initiating therapy under close supervision or with a low dose of an alternative angiotensin II antagonist

*** manufacturer recommends correcting condition prior to initiating treatment with valsartan or initiating therapy under close medical supervision.

PRODUCT AVAILABILITY: Telmisartan received FDA approval in November 1998. Telmisartan is available as 40 and 80 mg tablets. Telmisartan tablets are hygroscopic and require protection from moisture. They are individually blister-sealed in cartons of 28 tablets in rows of seven tablets labeled according to the days of the week. The tablets should not be removed from the blisters until immediately prior to administration. Table 5 compares the available dosage forms for the angiotensin receptor antagonists. A combination product with telmisartan and hydrochlorothiazide is being developed.

Table 5: Available Dosage Forms of the Available Angiotensin II Receptor Antagonists:

Drug	Strengths available	Tablet/Capsule
Candesartan	4, 8, 16 and 32 mg	Unscored Tablet
Irbesartan	75, 150 and 300 mg	Unscored Tablet
Losartan	25, 50 mg	Unscored Tablet
Telmisartan	40, 80 mg	Scored Tablet*
Valsartan	80, 160 mg	Capsule

* The telmisartan tablet has a decorative score. It may be possible to split the tablet immediately prior to administration. These tablets are extremely susceptible to moisture, so the other half of the tablet would have to be discarded rather than saved for a later dose.

Micardis 40 and 80mg tablets $1.28 per tablet AWP
Diovan with and without HCTZ 80 and 160mg $1.21 per capsule AWP
Avapro 75mg $1.17 per tablet, 150mg $1.25 per tablet and 300mg $2.19 per tablet AWP
Atacand 4,8 and 16mg $1.20 per tablet and 32mg $1.68 per tablet AWP

CONCLUSION: Telmisartan is another angiotensin II AT_1 receptor antagonist. It provides an alternative to candesartan, irbesartan, losartan and valsartan, but at this time demonstrates no apparent advantage over these agents. Like the other agents in this class, telmisartan is only approved for the treatment of hypertension. It is unknown whether telmisartan will be as effective as angiotensin converting enzyme inhibitors in the treatment of congestive heart failure or prevention of proteinuria in patients with diabetes.

NIACIN EXTENDED RELEASE TABLETS - NIASPAN by KOS PHARMACEUTICALS

A hydro-gel programmed release once-a-night controlled release niacin formulation.

INDICATIONS: Niaspan is indicated in the following patients
1.adjunct to diet for the reduction of elevated total cholesterol, LDL-C, Apo B, and triglyceride levels in adults with primary hypercholesterolemia and mixed dyslipidemia (Types IIa and IIb).
2. in combination with a bile-acid resin and as an adjunct to diet for elevated TC and LDL-C in adults with primary hypercholesterolemia (Type IIa).
3. as adjunctive therapy for treatment of adults with very high triglyceride levels (Type IV and V).
4. in patients with a history of MI and hypercholesterolemia, to reduce the risk of recurrent non-fatal MI.
5. in patients with a history of coronary artery disease and hypercholesterolemia, in combination with a bile-acid binding resin, to slow progression or promote regression of atherosclerotic disease.

PHARMACOKINETICS:

Niaspan Dose/day	given as	Peak conc. (ug/ml)	Time to peak (hrs)
1000mg	2x500mg	0.6	5
1500mg	2x750mg	4.9	4
2000mg	2x1000mg	15.5	5

The metabolic pathways of niacin are saturable which explains the nonlinear relationship between niacin dose and plasma concentration. The manufacturer recommends that patients take Niaspan at bedtime with a low fat snack to reduce GI distress and maximize bioavailability. Women have higher plasma levels and greater lipid lowering effects from equivalent doses than men.

CLINICAL STUDIES:
The Coronary Drug Project completed in 1975 enrolled men aged 30 to 64, who had a history of MI to either niacin (1119 patients) or placebo (2789 patients). After 5 years the incidence of definite, non-fatal MI was 8.9% in the niacin group vs. 12.2% in the placebo group ($p<0.004$) ARR 3.3%, NNT -30. Total mortality at 5 years was not significantly different 24.4% vs. 25.4%. A further 15 year follow-up found 11% or 69 fewer deaths in the niacin group compared to placebo (52% vs. 58.2%; $p=0.0004$). The trial was not designed to look at the 15 year mortality rate, most patients had not received niacin for the last 9 years and confounding variables were not controlled for. (JAMA 1975;231:360-81 and J Am Coll Cardiol 1986;8:1245-55)

Table 2. Efficacy between Niaspan, Immediate-Release Niacin and Placebo

Mean Percent Change from Baseline						
Parameter (mg/dL)	Niaspan N=76		IR Niacin N=74		Placebo N=73	
	Week 8 1500mg	Week 16 1500mg	Week 8 1500mg	Week 16 3000mg	Week 8 0mg	Week 16 0mg
LDL	-10.4	-10.9	-12.3	-19.8	0.9	0.6
Apo B	-10.9	-12.2	-11.9	-21.0	0.9	1.3
HDL	18.2	17.1	18.7	25.7	0.4	1.7
Triglycerides	-14.3	-10.7	-17.3	-26.5	6.3	10.5
Lp(a)	-17.3	-14.9	-10.1	-24.7	0.4	2.2

TABLE 6.—LIPID RESPONSE TO NIASPAN® THERAPY IN DOSE-ESCALATION STUDY[5,6]

	Mean Percent Change From Baseline*							
	TC	LDL-C	HDL-C	TC/HDL-C	TGs	Lp(a)	Apo B	Apo A1
Placebo† (n=44)	-2	-1	+5	-7	-6	-5	-2	+4
NIASPAN® (n=87)								
500 mg qhs	-2	-3	+10	-10	-5	-3	-2	+5
1000 mg qhs	-5	-9	+15	-17	-11	-12	-7	+8
1500 mg qhs	-11	-14	+22	-26	-28	-20	-15	+10
2000 mg qhs	-12	-17	+26	-29	-35	-24	-16	+12
2500 mg qhs‡	-16	-22	+30	-34	-39	-30	-22	+12
3000 mg qhs‡	-16	-21	+30	-35	-44	-26	-20	+12

*For all NIASPAN® doses except 500 mg, mean percent change from baseline was significantly different ($p<0.05$) from placebo for all lipid parameters shown except Lp(a) and Apo A1, which were significantly different from placebo starting with 1500 mg and 2000 mg, respectively.
†Placebo data shown are after 24 weeks of placebo treatment.
‡Outside normal recommended dosage range.

TABLE 7.—EFFECT OF GENDER ON NIASPAN® DOSE RESPONSE[6]

	Mean Percent Change From Baseline*							
	LDL-C		HDL-C		TGs		Apo B	
	M	F	M	F	M	F	M	F
500 mg qhs (50M/37F)	-2	-5	+11	+8	-3	-9	-1	-5
1000 mg qhs (76M/52F)	-6*	-11*	+14	+20	-10	-20	-5*	-10*
1500 mg qhs (104M/59F)	-12	-16	+19	+24	-17	-28	-13	-15
2000 mg qhs (75M/53F)	-15	-18	+23	+26	-30	-36	-16	-16

*Percent change significantly different between genders ($p<0.05$).

TABLE 8.—LONG-TERM EFFICACY OF NIASPAN®[6]

Treatment	Duration	n	Mean Percent Change From Baseline						
			TC	LDL-C	HDL-C	TC/HDL-C	TG	Lp(a)†	Apo B†
NIASPAN® alone	96 weeks	225	-13	-20	+28	-31	-28	-40	-17
NIASPAN® + HMG-CoA reductase inhibitor*	96 weeks	122	-27	-36	+27	-41	-35	-41	-30
NIASPAN® + BAS	96 weeks	9	-14	-25	+26‡	-30	+8§	-39	-21

All results are statistically significant ($p<0.001$) unless otherwise noted.
*NIASPAN® is indicated for concomitant use with BAS in conjunction with diet. (See WARNINGS, *Skeletal Muscle*, in Prescribing Information.)
†Analyzed in a subset of patients (n=73, 36, and 7) at 96 weeks.
‡$p\leq0.01$.
§Not statistically significant.

PRECAUTIONS:

Niaspan should not be used in patients who have liver problems and should be used with caution in patients who consume substantial amounts of alcoholic beverages. Fewer than 1% of patients discontinued Niaspan because of AST or ALT elevations >2 x ULN in controlled trials. All elevations were reversible upon discontinuation. Serum transaminase levels should be monitored before Niaspan and every 6 to 12 weeks for the first year. Niaspan should not be substituted for immediate release niacin, patients should be started on the lowest dose of Niaspan and titrated to the desired response. Niacin can increase serum uric acid levels, produce a dose related reduction in platelets (upto 11%), increase prothrombin time about 4%, and produce dose related reductions in phosphorus levels (about 13%). Watch for myositis and rhabdomyolysis with niacin especially when used in combination the a statin.

ADVERSE EFFECTS:

TABLE 9.—TREATMENT-EMERGENT ADVERSE EVENTS BY DOSE LEVEL IN ≥5% OF PATIENTS (CONSIDERED AT LEAST REMOTELY DRUG-RELATED) DURING PLACEBO-CONTROLLED NIASPAN® STUDIES*‡

			Recommended Daily Maintenance Doses			Outside of Recommended Daily Doses	
Event	Placebo (n=157)	500 mg (n=87)	1000 mg (n=110)	1500 mg (n=136)	2000 mg (n=95)	2500 mg (n=49)	3000 mg (n=46)
Headache	15%	5%†	9%	11%	8%	4%†	4%
Pain	3	1	2	5	3	0	2
Pain, abdominal	3	3	2	3	5	0	0
Diarrhea	8	6	7	6	8	10	11
Dyspepsia	8	2	4	5	5	6	0
Nausea	4	2	5	3	8	10	4
Vomiting	2	0	2	3	8†	8	2
Rhinitis	7	2	5	4	3	0	0
Pruritus	1	6	<1	3	1	0	0
Rash	<1	5	5	4	0	0	0

Note: Percentages were calculated from the total number of patients in each column. Adverse events are reported at the lowest dose where they occurred.

*Pooled results from placebo-controlled studies (n=245); mean treatment duration 17 weeks. Number of NIASPAN® patients is not additive across doses.

† Significantly different from placebo ($p \leq 0.05$).

TABLE 10.—TREATMENT-EMERGENT CHANGES IN SELECTED LABORATORY PARAMETERS DURING PLACEBO-CONTROLLED NIASPAN® STUDIES[5]

			Recommended Daily Maintenance Doses			Outside of Recommended Daily Doses	
	Placebo (n=157)	500 mg (n=87)	1000 mg (n=110)	1500 mg (n=136)	2000 mg (n=95)	2500 mg (n=51)	3000 mg (n=49)
AST							
>Normal	6%	2%	5%	4%	13%	6%	4%
>1.3x ULN	1	1	1	1	5	4	4
>2x ULN	1	1	0	1	2	0	2
>3x ULN	0	0	0	0	0	0	0
ALT							
>Normal	6%	2%	5%	2%	9%	6%	2%
>1.3x ULN	1	1	2	1	2	4	0
>2x ULN	0	0	0	0	1	0	0
>3x ULN	0	0	0	0	0	0	0
Uric acid							
>Normal	4%	2%	4%	12%*	15%*	12%	14%*
>1.3x ULN	0	0	0	0	1	0	2
Phosphorus							
<Normal	3%	1%	9%*	14%*	25%*	22%*	12%*
<2.0 mg/dL	0	0	0	1	6*	0	0
Platelets							
<Normal	<1%	0	0	1%	3%	4%*	4%

Note: Percentages were calculated from the total number of patients in each column. Laboratory events reported while on the specified dose. Number of NIASPAN® patients is not additive across doses.
*Significantly different from placebo ($p \leq 0.05$).

DOSAGE:
Niaspan should be taken at bedtime, after a low-fat snack, and doses individualized based upon response. The recommended dosage schedule is as follows:

week 1. 375mg at bedtime
week 2. 500mg at bedtime
week 3. 750mg at bedtime (these doses are found in the 21 tablet titration starter pack at a cost of $10.00 AWP)
weeks 4 to 7. 1000mg (2x 500mg) at bedtime (500mg tablets $45.00/100 AWP)
after 7 weeks and not faster than 500mg per 4 week period the dosage can be increased to 1500mg at bedtime (2x 750mg) (750mg tablets $58.00/100 AWP)
the maximum daily dose is 2000mg at bedtime (1000mgx2) (1000mg tablets $65.83/100 AWP)

Aspirin 325mg given 30 minutes prior to Niaspan can significantly reduce the flushing that may commonly occur with niacin.

CONCLUSIONS: Niaspan appears to be an effective lipid lowering agent that is generally better tolerated that some of the other forms of niacin. Niaspan also appears to have a low risk of elevated transaminases. Niacin is a unique lipid lowering agent which has a beneficial effect on all components of the lipid profile including increasing HDL while lowering LDL, TG, TC, and Lp(a).

Comparison of Dose Dependent LDL Lowering Effects of HMG CoA Reductase Inhibitors			
HMG-CoA	**Daily Dose**	**Average LDL Reduction by Dose**	**(AWP/mth)**
lovastatin (Mevacor®)	10 mg qd	21%	$ 39.62
	20 mg qd	24-27%	$ 69.85
	40 mg qd	30-32%	$125.74
	40 mg bid	40-42%	$251.48
pravastatin (Pravachol®)	10 mg qd	22%	$ 60.32
	20 mg qd	32%	$ 64.95
	40 mg qd	34%	$106.77
simvastatin (Zocor®)	5 mg qd	24%	$ 53.42
	10 mg qd	33%	$ 62.99
	20 mg qd	33%	$109.88
	40 mg qd	40%	$109.88
	80 mg qd	46%	$109.88
fluvastatin (Lescol®)	20 mg qd	20-25%	$ 37.64
	40 mg qd	24-31%	$ 42.09
	40 mg bid	34-35%	$ 84.18
atorvastatin (Lipitor®)	10 mg qd	39%	$ 54.72
	20 mg qd	43%	$ 84.60
	40 mg qd	50%	$101.88
	40 mg bid	60%	$203.76
Cervistatin (Baycol®)	0.3 mg qd	28%	$ 39.60

(09/98 AWP)

ENOXAPARIN – LOVENOX (Rhone Poulenc Rorer)

INDICATIONS:

1. Prevention of DVT which may lead to pulmonary embolism in the following patients
   - hip replacement surgery both during surgery and after hospitalization
   - knee replacement therapy
   - abdominal surgery
2. Prevention of ischemic complications of unstable angina and non-Q-wave MI
3. Treatment of acute DVT and or PE in hospitalized patients
4. Outpatient treatment of DVT

Cost- 30mg amps $16.81 AWP
30mg syringe $17.65
40mg syringe $23.53
60mg syringe $35.33
80mg syringe $47.10
100mg syringe $58.88

A COMPARISON OF LOW-MOLECULAR-WEIGHT HEPARIN ADMINISTERED PRIMARILY AT HOME WITH UNFRACTIONATED HEPARIN ADMINISTERED IN THE HOSPITAL FOR PROXIMAL DEEP-VEIN THROMBOSIS

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Abstract *Background.* Patients with acute proximal deep-vein thrombosis are usually treated first in the hospital with intravenous standard (unfractionated) heparin. However, the longer plasma half-life, better bioavailability after subcutaneous administration, and more predictable anticoagulant response of low-molecular-weight heparins make them attractive for possible home use. We compared these two approaches.

Methods. Patients with acute proximal deep-vein thrombosis were randomly assigned to receive either intravenous standard heparin in the hospital (253 patients) or low-molecular-weight heparin (1 mg of enoxaparin per kilogram of body weight subcutaneously twice daily) administered primarily at home (247 patients). The study design allowed outpatients taking low-molecular-weight heparin to go home immediately and hospitalized patients taking low-molecular-weight heparin to be discharged early. All the patients received warfarin starting on the second day.

Results. Thirteen of the 247 patients receiving low-molecular-weight heparin (5.3 percent) had recurrent thromboembolism, as compared with 17 of the 253 patients receiving standard heparin (6.7 percent; $P=0.57$; absolute difference, 1.4 percentage points; 95 percent confidence interval, −3.0 to 5.7). Five patients receiving low-molecular-weight heparin had major bleeding, as compared with three patients receiving standard heparin. After randomization, the patients who received low-molecular-weight heparin spent a mean of 1.1 days in the hospital, as compared with 6.5 days for the standard-heparin group; 120 patients in the low-molecular-weight–heparin group did not need to be hospitalized at all.

Conclusions. Low-molecular-weight heparin can be used safely and effectively to treat patients with proximal deep-vein thrombosis at home. (N Engl J Med 1996;334: 677-81.)

TREATMENT OF ACUTE DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Enoxaparin has recently been FDA approved for the treatment of DVT and PE

Approved regimens include the following:

1. Outpatients without PE who can be treated at home
   Enoxaparin 1mg/kg every 12 hours (initiate warfarin therapy early and overlap until INR is greater than 2 for 2 consecutive days).

2. Inpatient (hospital) treatment of patients with DVT with or without PE
   Enoxaparin 1.5mg/kg once a day and overlapped with warfarin as above.

   Enoxaparin is currently available in: 30mg amps; 30 and 40mg prefilled syringes; and 60, 80 and 100mg graduated syringes.

Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis and Pulmonary Embolism

	Dosing Regimen[1]		
Indication	Lovenox 1.5 mg/kg q.d. SC n (%)	Lovenox 1.0 mg/kg q12h SC n (%)	Heparin aPTT Adjusted i.v. Therapy n (%)
All Treated DVT Patients with and without PE	298 (100)	312 (100)	290 (100)
Patient Outcome Total VTE[2] (%)	13 (4.4)[3]	9 (2.9)[3]	12 (4.1)
DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)
Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)
PE (%)	2 (0.7)	2 (0.6)	4 (1.4)

[1] All patients were also treated with warfarin sodium commencing within 72 hours of Lovenox or standard heparin therapy.
[2] VTE = venous thromboembolic event (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]).
[3] The 95% Confidence Intervals for the treatment differences for total VTE were:
Lovenox once a day versus heparin (-3.0 to 3.5)
Lovenox every 12 hours versus heparin (-4.2 to 1.7).

Table 5—*Guidelines for Anticoagulation: LMW Heparin

	Guidelines
Disease suspected:	• Obtain baseline APTT, PT, CBC
	• Check for contraindication to heparin therapy
	• Give unfractionated heparin 5,000 U IV and order imaging study
Disease confirmed:	• Give LMW heparin (enoxaparin) 1 mg/kg subcutaneously q12h
	• Start warfarin therapy on day 1 at 5 mg and adjust the subsequent daily dose according to INR
	• Consider checking a platelet count between days 3–5
	• Stop LMW heparin therapy after at least 4–5 days of combined therapy when INR is > 2.0 for 2 consecutive days
	• Anticoagulate with warfarin for at least 3 months at an INR of 2.0–3.0 (see Table 6)

* PT = prothrombin time.

Table 2: University of California at Davis Medical Center: DVT Therapy Costs for Standard Heparin Infusion vs LMWH (enoxaparin): 1995

Inpatient Costs for Heparin	
Average Length of Stay:	6.77 days
Hospital Cost/Admission:	$8,650.00
Daily Hospital Costs:	**$1,290.00/day**
Outpatient Costs for Enoxaparin	
Anticoagulation Clinic Visit:	$27.00
Drug Costs:	$57.40
Home Nursing:	$44.00
Lab Fees:	$15.00
Total Daily Costs:	$143.40/day
Cost Savings:	**$1,140.00/day**

Source: Richard H. White, MD, UC-Davis, as presented at the Society of General Internal Medicine 21st Annual Meeting, April 23-25, 1998.

Patient Selection for Ambulatory DVT Therapy

- patients with confirmed proximal DVT or symptomatic calf-vein thrombosis requiring anticoagulant therapy
- >12 years old and clinically stable
- exclusions:
    - recent history of GI bleed or PUD within 3-5 years
    - major surgery in last 2 weeks
    - use of NSAIDs (>325mg ASA/day)
    - renal dysfunction (creatinine clearance <30ml/min; serum creat. >2.5mg/dL
- Patients must be compliant and able to self-administer LMWH injections
- Patients must complete patient education program (~1 hr)
- Patients must have a telephone and be able to communicate with members of the health-care team
- Patients with suspected PE are treated as inpatients for 24-72 hours and then evaluated for home therapy
- Max. dose of enoxaparin is 90 mg BID, oral warfarin is also begun with a target INR of 2-3 (stockings and leg elevation are recommended)

During the first 18 months of the program, 66 patients were managed in this manner. Only one patient (stage III ovarian and endometrial cancer) failed therapy and one additional patient with rectal polyp surgery had a minor GI bleed.

Table 3: Home LMWH Therapy Compared to Inpatient Continuous Infusion: UC-Davis Medical Center

Continuous heparin	6.77 days
Enoxaparin	2.12 days
Decrease in LOS	4.65 days

66 patients x 4.65 days = 307 total days saved
Savings: $1,140 x 307 = $349,980 saved over 18 months

Source: Richard H. White, MD. UC-Davis, as presented at the Society of General Internal Medicine 21st Annual Meeting. April 23-25, 1998.

Outpatient DVT Program at Mt. Sinai Hospital
(Dr. Andrew Dunn; Society of General Internal Medicine 21st Annual Meeting 4/23-4/25/98)

Contraindications: active bleeding or familial bleeding disorder; inability of the patient or a family member to administer the medication or interact with the home health nurse; likely non-compliance; symptomatic PE; morbid obesity; pregnancy; NSAID use and length of stay >4 days.

Mount Sinai protocol: 84 mg enoxaparinSC q 12 h and oral warfarin 5 mg; continue both until INR of 2-3 for at least 2 consecutive days (minimum of 5 days combined therapy).

CLOPIDOGREL - Plavix® by Sanofi and Bristol-Myers Squibb - 1P

INDICATIONS: Clopidogrel is indicated for the reduction of atherosclerotic events (myocardial infarction, stroke and vascular death) in patients with atherosclerosis documented by recent myocardial infarction, recent stroke or established peripheral arterial disease. Ticlopidine is indicated only to reduce the risk of thrombotic stroke in patients who have experienced stroke precursors and in patients who have had a completed thrombotic stroke. In addition, because of the risk of neutropenia and agranulocytosis, use of ticlopidine should be reserved for patients who are intolerant to aspirin therapy.

CLINICAL PHARMACOLOGY: Clopidogrel, a thienopyridine related to ticlopidine, is a selective and irreversible inhibitor of ADP-induced platelet aggregation which is a result of irreversibly modifying the platelet ADP receptor and not the inhibition of phosphodiesterase (see Table 1). In vitro, both ticlopidine and clopidogrel are inactive. Activity is only shown after in vivo administration, indicating the drugs must be activated, probably by the CYP enzymes of the liver. Like ticlopidine, clopidogrel inhibits platelet aggregation and increases bleeding time. Clopidogrel is 40 to 100 times more potent than ticlopidine. Like aspirin, clopidogrel's effects on the platelet are irreversible for the remainder of the platelet's lifespan.

Table 1: Mechanisms for the Inhibition of Platelet Activity:

Agent	ADP-Receptor Site Modification	Inhibiting ADP-Induced Platelet-Fibrinogen Binding	Cyclooxygenase Inhibition	Phosphodiesterase Inhibition
Aspirin			X	
Clopidogrel	X			
Dipyridamole				X
Ticlopidine		X		
Sulfinpyrazone			X	

Inhibition of ADP-induced platelet aggregation from 12% to 42% occurs 2 hours after single doses of 100 to 600 mg of clopidogrel, and these effects are maintained for at least 48 hours. Bleeding time is prolonged within 1 hour of a 375 mg dose. After receiving clopidogrel 50 to 100 mg daily, the platelet aggregation averaged 50% after 4 to 7 days of therapy, and there was a 2-fold prolongation of bleeding time. After discontinuation of clopidogrel therapy, platelet aggregation and bleeding time gradually return to baseline within 5 days.

PHARMACOKINETICS: Clopidogrel is rapidly absorbed after oral administration and is unaffected by food. Clopidogrel activation is dependent on metabolic activation via the hepatic cytochrome P450 1A isozymes. Administration with

agents inhibiting this pathway results in reduced antiaggregating activity, while administration with inducing agents increases the activity. CYP 2B metabolizes clopidogrel to inactive metabolites.

COMPARATIVE EFFICACY: The landmark study evaluating clopidogrel is a trial known as CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events). In this randomized, double-blind study clopidogrel 75 mg once daily and aspirin 325 mg once daily were compared to determine their relative efficacy in reducing the risk of a composite outcome cluster of ischemic stroke, myocardial infarction or vascular death. The study enrolled 19,185 patients with recent ischemic stroke, recent myocardial infarction or symptomatic peripheral vascular disease who were followed from 1 to 3 years. At the time the data were analyzed, the mean treatment period was 1.91 years and treatment cohort consisted of 9,577 patients receiving clopidogrel and 9,566 patients receiving aspirin therapy. Outcome events occurred in 1,171 patients in the clopidogrel group and 1,236 patients in the aspirin group. (The product labeling indicates that outcome events occurred in 939 patients receiving clopidogrel and 1,020 patients receiving aspirin.) Patients treated with clopidogrel had a 5.32% risk of ischemic stroke, myocardial infarction or vascular death, compared with a 5.83% risk with aspirin in the intended-to-treat cohort. The product labeling indicates that the incidence of ischemic stroke was 4.56% and 4.81%, respectively; fatal and non-fatal myocardial infarction was 2.86% and 3.47%, respectively; and other vascular deaths occurred in 2.35% and 2.36%, respectively. The absolute risk reduction was 0.51%. (The difference reported in the product labeling is 0.86%). Overall relative risk was reduced 8.7% in favor of clopidogrel ($p = 0.045$). This means that 19 major events could be prevented with aspirin and 24 major events could be prevented with clopidogrel for each 1,000 patients treated for 1 year. Only overall risk reduction and risk reduction among patients with peripheral arterial disease were significantly reduced with clopidogrel compared to aspirin. Differences in the frequency of outcome events for patients with stroke or myocardial infarction did not differ between treatments. Additional results are presented in Table 2. The overall incidence of adverse effects was the same in both groups, although rash and diarrhea occurred more frequently in the clopidogrel group while upper gastrointestinal discomfort and gastrointestinal hemorrhage tended to occur more frequently in the aspirin group.

Table 2: Treatment Effect by Subgroup from the CAPRIE Study

Subgroup and treatment group	Event rate per year	Realtive-risk reduction with clopidogrel	p value
Stroke			
Clopidogrel	7.15%	7.3%	0.26
Aspirin	7.71%		
Myocardial Infarction			
Clopidogrel	5.03%	-3.7%	0.66
Aspirin	4.84%		
Peripheral Arterial Disease			
Clopidogrel	3.71%	23.8%	0.0028
Aspirin	4.86%		
All Patients			
Clopidogrel	5.32%	8.7%	0.043
Aspirin	5.83%		

Clopidogrel and ticlopidine were compared in 150 patients with peripheral arterial disease or cardiac or cerebral manifestations of atherosclerosis to determine the optimal dose of clopidogrel for the CAPRIE trial. Patients received clopidogrel 10, 25, 50, 75 or 100 mg once daily, ticlopidine 250 mg twice daily or placebo for 28 days. Dose-related inhibition of platelet aggregation and bleeding time prolongation were observed with clopidogrel. Clopidogrel doses of 50 to 100 mg and the ticlopidine produced comparable inhibition in ADP-induced platelet aggregation and prolongation of bleeding times by a factor of 1.5 to 1.9.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS: Clopidogrel is contraindicated in patients with active pathologic bleeding or who have shown hypersensitivity to any components of the product. Clopidogrel should be used with caution in patients with severe liver disease. The contraindications and warning associated with clopidogrel and ticlopidine are summarized in Table 3.

There have been no reports of tumorigenicity, genotoxicity or changes in fertility with clopidogrel in various animal models. Its use in pregnancy has been classified as Category B.

Table 3: Comparative Contraindications, Warnings and Precautions with Clopidogrel and Ticlopidine

	Clopidogrel		Ticlopidine	
Contraindications				
Hypersensitivity to the drug		X		X
Presence of a hemostatic disorder or active pathological bleeding	X		X	
Patients with severe liver impairment			X	
Presence of hematopoietic disorders such as neutropenia and thrombocytopenia			X	
Warnings & Precautions				
Neutropenia			X	
Thrombocytopenia				X
Other hematological effects			X	
Increased cholesterol levels			X	
Use with other anticoagulant drugs	X		X	
Use with other antiplatelet drugs	X		X	

ADVERSE REACTIONS: The side effects most frequently observed have included indigestion, nausea, bleeding disorders, rash, diarrhea and pruritus. The incidence of gastrointestinal bleeding is 2% with clopidogrel and 2.7% with aspirin. A summary of some of the adverse effects experienced during the CAPRIE study can be found in Table 4. A complete list of side effects reported with clopidogrel therapy can be found in the product labeling.

Table 4: Comparison of Selected Adverse Effects Reported in the CAPRIE Study

	Aspirin	Clopidogrel
Chest pain	8.3%	8.3%
Headache	7.2%	7.6%
Abdominal pain	7.1%	5.6%
Dizziness	6.7%	6.2%
Dyspepsia	6.1%	5.2%
Hypertension	5.1%	4.3%
Edema	4.5%	4.1%
Hypercholesterolemia	4.4%	4%
Nausea	3.8%	3.4%
Purpura	3.7%	5.3%
Rash	3.5%	4.2%
Diarrhea	3.4%	4.5%
Fatigue	3.4%	3.3%
Epistaxis	2.5%	2.9%
Pruritus	1.6%	3.3%

Rates of severe rash, severe diarrhea and neutropenia in the CAPRIE trial were lower than those observed in ticlopidine studies.

DRUG INTERACTIONS: In animal studies, aprotinin reduces the prolongation of bleeding time associated with clopidogrel and may be useful in reducing bleeding risk associated with procedures in patients receiving clopidogrel or ticlopidine therapy.

Aspirin does not increase platelet aggregation or bleeding time when used in combination with clopidogrel. Administration of clopidogrel with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin or warfarin should be done with caution until more information is available. Administration with heparin with clopidogrel does not alter heparin consumption, bleeding time, platelet aggregation and activated partial thromboplastin time (APTT) ratio; however, the safety of this combination has not been adequately evaluated. Coadministration of clopidogrel with atenolol, nifedipine, phenobarbital, cimetidine or digoxin is not associated with a pharmacodynamic drug interaction, nor does clopidogrel influence the elimination of theophylline or digoxin.

Since clopidogrel inhibits CYP 2C9 in vitro, it might interfere with the elimination of drugs metabolized by this enzyme (eg, phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin and NSAIDs).

RECOMMENDED MONITORING: Patients treated with ticlopidine must have a complete blood count, including platelet count and white cell differential, prior to therapy and every 2 weeks during the first 3 months of therapy. This type of monitoring is not required with clopidogrel or aspirin therapy. All patients receiving antiplatelet medications should be monitored for signs and symptoms of bleeding.

DOSING: The recommended initial dose of clopidogrel is 75 mg once daily with or without food. No adjustment in dosing needs to be made for age, race, gender or renal dysfunction.

Clopidogrel should be discontinued 7 days prior to any elective surgical procedures where an antiplatelet effect is not desired.

Safety and effectiveness in children have not been established.

COST: 75 mg $2.40/tab AWP

CONCLUSION: Clopidogrel is an effective agent in the prevention of atherosclerotic events (myocardial infarction, stroke and vascular death) in patients with atherosclerosis documented by recent myocardial infarction, recent stroke or established peripheral arterial disease. It should be considered an alternative to aspirin and ticlopidine. It appears to be slightly more effective than aspirin. It is not clear if any special patient population will get a better protection rate from clopidogrel than aspirin or ticlopidine. The side effects associated with clopidogrel therapy are similar to those reported with aspirin, and clopidogrel causes less neutropenia than ticlopidine.